REMARKS

1. History/Elections

Applicants thank Examiner Gangle for the teleconference on August 31, 2006. During that teleconference, Applicants and Examiner Gangle discussed the objection to claims 37-45, 47-48, 50, 55, 58-60, and 62-67 being drawn, at least in part, to non-elected species. Examiner Gangle indicated that the restriction requirement had required Applicants to elect species. Under that procedure, Applicants had properly elected the species and that the claims as pending were proper. Examiner Gangle stated that the objection would be withdrawn, and the claims would be examined as presently presented. Applicants again thank the Examiner for his time on this matter.

The outstanding issues in the outstanding office action are addressed individually below.

2. Claim Objections

Claims 37-45, 47-48, 50, 55, 58-60, and 62-67 were objected to as allegedly being drawn, in part, to non-elected species. As determined during the teleconference with Examiner Gangle, Applicants respectfully assert that, in a species election as was requested by the Restriction Requirement, it is appropriate to include a non-elected species in an unrelated claim that may cover the non-elected species.

Accordingly, Applicants respectfully request that the objection be reconsidered and withdrawn.

Claim 58 was further objected to as allegedly containing a typographical error. Applicants have amended Claim 58 to eliminate the error.

3. Claim Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 37-45, 47-48, 50, 55, 58-60, and 62-67 were rejected as failing to comply with 35 U.S.C. § 112, first paragraph, for failing to describe the subject matter of the claimed invention in such a way as to reasonably convey to one of skill in the art that the inventors were in

possession of the claimed invention at the time the application was filed. Applicants respectfully traverse this rejection.

According to MPEP § 2163, an applicant shows possession of the claimed invention by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention (*see also Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 68 (1998).

Applicants respectfully aver that the specification provides sufficient distinguishing characteristics for vaccine compositions comprising antigens or allergens other than tetanus toxoid. For instance, the specification discloses that the antigen is derived from a pathogen and lists a group of pathogens by which the antigen can be derived (see pg. 24). Additionally, an antigen is described as being a part of a pathogen that can be administered in the system to induce antibody production (see pg. 10). Compounds are taught that are isolated from the pathogens disclosed in the specification, including lipids, carbohydrates, and proteins (see pg. 25). Therefore, the specification discloses the organisms from which antigens can be isolated, and teaches the types of molecules that comprise antigens. Thus, the specification provides more than adequate written description for vaccines comprising antigens other than tetanus toxoid.

Accordingly, Applicants respectfully request that this written description rejection be reconsidered and withdrawn.

Claims 37-45, 47-48, 50, 55, 58-60, and 62-67 were also rejected under 35 U.S.C. § 112, first paragraph, as not enabling one of skill in the art to make and use the claimed invention. Specifically, the Office Action states that the specification does not provide enablement for vaccines other than those vaccines comprising an antigen derived from tetanus toxoid. Applicants respectfully traverse this rejection.

According to MPEP § 2164.01, a claimed invention must be enabled so that any person skilled in the art can make and use the invention without undue experimentation. The fact that experimentation may be complex does not make it undue, especially if the art typically engages in such experimentation (MPEP § 2164.01). The test of enablement is not whether any experimentation is necessary, but whether it is undue (MPEP § 2164.01). Moreover, the quantity of experimentation is not undue "since a considerable amount of experimentation is permissible, if it is routine, or if the specification in question provides a reasonable amount of guidance with

respect to the direction in which the experimentation should proceed" (MPEP § 2164.06; *quoting, In re Wands,* 858 F.2d 731, 737 (Fed. Cir. 1988).

Applicants respectfully assert that the specification amply enables the making and use of the vaccine compositions of the claims because the experiments for determining whether an antigen produces protective immunity require only routine experimentation in light of the disclosure in the specification and the knowledge in the art. For example, the specification provides working examples of how to make and use a vaccine from tetanus toxoid (see Examples 1-28). It provides detailed examples of how to introduce an antigen into an organism and how to measure the immune response thereto (see Examples 11-15). Furthermore, specific compositions for non-invasive vaccination through the skin are disclosed (see Examples 1-13). The specification also provides sufficient disclosure of other pathogens and the range of compounds derived from such pathogens that could generate an immune response (see specification, pg. 24). Thus, one with skill in the art can practice the invention by merely exchanging one antigen for another, using the teachings in the specification of how to make the compositions and how to determine whether the particular compound generates an immune response. Moreover, those of skill in the art recognize that new technologies have allowed vaccine researchers to produce proteins quickly for vaccine testing (see, *e.g.*, Ellis, Ch. 29, Vaccines. Plotkin and Mortimer (eds.), 1988 (see pg. 571). Thus, it would require only routine experimentation to identify antigens other than tetanus toxoid and make vaccine compositions containing those compositions.

Accordingly, Applicants respectfully request that this enablement rejection be reconsidered and withdrawn.

4. Claim Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 37-45, 47-48, 50, 55, 58-60, and 62-67 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to point out and distinctly claim the subject matter which the applicant regards as the invention. Applicants respectfully traverse these rejections, in part, as explained individually below.

Claim 37 was rejected as being vague and indefinite because of recitation of the phrase "the penetrant in the form of a minute droplet surrounded by a coating of one or more layers of at least 2 substances that differ by at least a factor of 10 in solubility in a liquid medium" (see

Office Action, pg. 8). Specifically, the Office Action alleges that it is unclear how anything could have a solubility in something other than a liquid medium (see Office Action, pg. 8).

In response, simply to facilitate prosecution and not in acquiescence to the rejection, Applicants have amended Claim 37 to remove the term "in a liquid medium."

The Office Action also states that it is not clear how one can have a layer of two substances (see Office Action, pg. 8). Applicants aver that a layer can be composed of one or more substances. For instance, a layer can be composed of a combination of a lipid and a surfactant. One of skill in the art would understand from the claim that the coating can have more than one layer, and each layer can include at least two substances (see Specification, pg. 7, fourth paragraph). The specification also discloses vesicles (*i.e.*, penetrants) having a coating comprising a first substance that is more soluble (*i.e.*, as surfactant) and a second substance that is less soluble (*i.e.*, a lipid) (see Specification, pg. 15 first paragraph; pg. 22, last paragraph; and pg. 33, first paragraph). Accordingly, Applicants aver that this phrase clearly and distinctly points out the subject matter that is the claimed invention.

Additionally, Claim 37 was rejected for the recitation "the penetrant is in the form of." Applicants have amended Claim 37 to recite that "the penetrant being in the form of a minute fluid droplet surrounded by a coating..." This phrase informs one of skill in the art that the penetrant is in a form in which it is the minute droplet *and* the coating. The specification also describes a non-limiting embodiment where the penetrant is in the form of a minute fluid droplet surrounded by a membrane-like coating of one or several layers of at least two different substances (see Specification, pg. 7, fourth paragraph). In other exemplary embodiments, penetrants are vesicles comprising bi-component (*i.e.*, two substances) immuno-aggregates in the form of vesicles with a highly flexible membrane and oligobilayer (*i.e*, coating) vesicles that comprise at least two substances (see Specification, pg. 18, second paragraph and pg. 32, second paragraph). Accordingly, Applicants aver that this phrase clearly and distinctly points out the subject matter that is the claimed invention.

Claim 37 was also rejected for the recitation that the composition comprises "an antigen or allergen." Applicants aver that the claim is not rendered vague and indefinite merely by not reciting the exact location of the antigen or allergen. One of skill in the art would understand that the antigen or allergen is mixed with the penetrant to allow for movement across a barrier.

Accordingly, Applicants respectfully request that this rejection be reconsidered and withdrawn.

Claim 37 was also rejected as being vague and indefinite by recitation of the phrase "an antigen or mixture thereof." The Office Action alleges that the phrase is vague because it is not clear to what mixture of antigens Applicants are referring, and it is not clear whether the vaccine contains a single antigen or mixtures of the antigen or a mixture of antigens.

Applicants respectfully aver that one of skill in the art would understand the statement to mean that the vaccine composition can contain an antigen or mixtures of different antigenic compounds. The term "or" means that the invention can be either an antigen or a mixture of antigens. The specification defines the terms "antigen" and "allergen" to include a wide range of different compounds (see Specification, pg. 10, fourth paragraph and pg. 9, third paragraph). Furthermore, claims 47 and 48 list a group of pathogens that can yield antigenic compounds. In addition, vaccines with combinations of antigens are well known in the art, *e.g.*, the mumps, measles, and rubella vaccine (see Freeman *et al.* (1993) *CMAJ.* 149(11): 1669-74). In addition, the specification discloses embodiments in which the transdermal vaccine can comprise "a mixture of antigens and/or a mixture of allergens" (see Specification, pg. 8, first paragraph). Therefore, one of skill in the art would comprehend the subject matter of the claimed invention. However, simply to facilitate prosecution, Claim 37 has been amended to recite "an antigen or mixture of different antigens, and/or an allergen or mixture of different allergens." Support for this amendment can be found *inter alia* in claims 47-48 in the specification at page 8, first paragraph; page 9, second paragraph; and page 10, fourth and fifth paragraph.

Likewise, 38-45, 47, 48, 50, 55, and 58-60, which are dependent on Claim 37 and thus contain all the limitations thereof, are not indefinite.

Accordingly, Applicants respectfully request that this indefiniteness rejection of Claim 37 be reconsidered and withdrawn.

Claim 38 was rejected as being vague and indefinite because of the phrase "wherein the at least two substances are two different forms of a substance." The Office Action alleges that it is not clear what the two different forms of the substance are.

Applicants respectfully aver that Claim 38 is not vague and indefinite. Nevertheless, Applicants have amended Claim 38 to expedite prosecution without acquiescing to the rejection. Amended Claim 38 now clearly indicates that the "at least two substances are two ionization states or salt forms of the same substance." Support for the amendment is found *inter alia* at page 13 of the specification.

Accordingly, Applicants respectfully request that the indefiniteness rejection of Claim 38 be reconsidered and withdrawn.

Claim 39 was rejected as being vague and indefinite because of the phrase "the antigen or allergen are associated with the penetrant." The Office Action states that it is unclear what other forms of association there can be between the antigen or allergen and the penetrant than those disclosed in Claim 37.

Applicants respectfully assert that the claim distinctly discloses the invention. The term "associated" has a common usage that is similar to the term "association," which is used to describe a type of interaction between molecules. The term "association" is used within the field of chemistry to mean a "combination, connection, or correlation of substances..." (see Grant & Hackh's Chemical Dictionary, 5th Ed., Grant and Grant, eds., McGraw-Hill, Inc., New York, 1987). The specification discloses methods of combining a suspension of antigen-free penetrants with antigen to allow such substances to associate (see Specification, pg. 27, sixth paragraph). The specification also incorporates by reference art teaching methods to induce the association between the substances (PCT/EP98/06750 (incorporated by reference), pg. 24, second paragraph). The specification further supports this definition of being combined or connected by describing that an immunogen is an antigen that is "free or associated with a carrier" (see Specification, pg. 13). Moreover, the specification teaches that a penetrant can comprise membranes that interface with a liquid medium (see PCT/EP98/06750, pg. 20, second paragraph). In these embodiments, the allergens and antigens associate with the penetrant by inserting into the interface between the membrane and the liquid medium (see PCT/EP98/06750, pg. 20, second paragraph). Thus, the term "associated" is meant to encompass "combined or connected physically with the penetrant," rather than being free in the penetrant composition.

Claim 37 recites that the composition comprises an antigen or mixtures thereof, and/or an allergen, or mixtures thereof. How the antigen and/or allergen interact with the penetrant other

than being mixed with the penetrant is not a limitation of this claim. However, Claim 39, which is dependent on Claim 37, includes the limitation that the antigen and/or allergen must be associated with the penetrant. One of skill in the art would understand what the distinction of Claim 39 is over Claim 37.

Accordingly, Applicants respectfully request that this rejection be reconsidered and withdrawn.

Claims 40, 58, and 59 were rejected as being vague and indefinite due to the phrase "surfactant-like molecule."

Applicants respectfully aver that the phrase is not vague and indefinite. However, solely to facilitate prosecution, Applicants have amended Claims 40, 58, and 59 to remove the phrase. The remaining term, "surfactant" refers to any molecule that acts like a surfactant or has surfactant-like properties (*see,* Specification, page 15).

Accordingly, Applicants respectfully request that the indefiniteness rejection of Claims 40, 58, and 59 be reconsidered and withdrawn.

Claim 42 was rejected as being vague and indefinite due to recitation of the phrase "wherein the total weight of droplets in the vaccine for use on human or animal skin is 0.01 weight-% (w-%) to 40 w-% of total mass."

Applicants respectfully assert that the claim as presently amended is not vague and indefinite. However, solely to facilitate prosecution, Applicants have amended Claim 42 to recite that the "wherein the total weight of droplets in the vaccine for use on human or animal skin is 0.01 weight-% (w-%) to 40 w-% of total mass of the vaccine." Support for the amendment is found *inter alia* at page 23 of the specification. Applicants aver that the Claim 42, as amended, now clearly delineates that the droplets weight is related to the total mass of the vaccine.

Accordingly, Applicants respectfully request that the indefiniteness rejection of Claim 42 be reconsidered and withdrawn.

Claim 47 was rejected as being vague and indefinite due to the phrase "derived from."

Applicants respectfully aver that the phrase is not vague and indefinite, because it has an ordinary meaning well known to those of skill in the art. The term "derived" means "to receive

or obtain from a source" (see Webster's Dictionary, 3rd Ed., Random House, New York, 1998). The phrase "derived from" in the context of Claim 47 therefore means that the antigen is obtained from a pathogen.

Accordingly, Applicants respectfully request that this indefiniteness rejection be reconsidered and withdrawn.

Claim 48 was rejected as being vague and indefinite for recitation of the phrase "pathogens triggering tetanus." The Office Action states that it is not clear what organisms other than *Clostridium tetani* the claim is referring to.

Applicants respectfully assert that the claim as presently amended is not vague and indefinite. However, solely to facilitate prosecution, Applicants have amended Claim 48 to recite "negative bacteria,..., *Clostridium tetani*,..." in place of the phrase at issue. Support for the amendment is found *inter alia* at page 24, first paragraph, of the specification. Applicants respectfully request that the indefiniteness rejection of Claim 48 be reconsidered and withdrawn.

Claim 50 was rejected as being vague and indefinite due to recitation of the phrase "wherein the concentration of each compound used." The Office Action alleges that it is not clear what compound the claim is referring to. Applicants traverse this rejection.

Applicants respectfully aver that the phrase is not vague and indefinite. The term "compound" is recited in Claim 37, from which Claim 50 depends and is used step b) to describe those compounds that have, or induce, cytokine or anti-cytokine activity. It is not used to describe any other vaccine component. Claim 50 uses the term "each" in combination with the term "compound" to indicate to one skilled in the art that it is referring to "each compound" described previously in Claim 37. Therefore, Applicants aver that Claim 50 is not vague and indefinite, and so respectfully request that this rejection be reconsidered and withdrawn.

Claims 44, 58, and 60 were rejected as being vague and indefinite due to recitation of the term "low molecular weight irritant." The Office Action alleges that the term low is not defined in the claim or the specification to provide the requisite degree so that one of skill in the art would be apprised of the scope of the claims. Applicants traverse this rejection.

Applicants respectfully assert that this term is sufficiently described in the specification and would be immediately known to one of ordinary skill in the art. Those of skill in the art use

the term "low molecular weight" commonly to refer to molecules that are of lower molecular weight than other molecules within a particular class (see, *e.g.*, Arts *et al.* (1998) *Toxicol Appl Pharmacol.* 152(1): 66-76 (studying the effect of "low molecular weight chemicals" on allergic inflammatory airway reactions and airway morphology and functionality); Frew *et al.* (1996) *Toxicol Lett.* 86(2-3): 65-72 (reviewing studies on the effects of low molecular weight chemicals on respiratory allergies); Tosti *et al.* (1993)*Toxicol Ind Health.* 9(3): 493-502 (studying the effects of allergenic low molecular weight oligomers on skin); Dearman *et al.* (1991) *Int Arch Allergy Appl Immunol.* 95(1): 70-6)). One of skill in the art would therefore realize that the term "low molecular weight irritants" comprised a group of compounds that include molecules of low molecular weight as compared to large protein irritants known in the art (see. *e.g.*, Meggs (1999) *Toxicol. Ind. Health.* 15(3-4): 331-8).

Furthermore, the specification describes a "low molecular weight irritant" as classes of allergenic metal ions, acids, bases, irritating fluids, (fatty-) alcohols, (fatty-) amines, (fatty-) ethers, (fatty-) sulphonates, -phosphates, etc., or other suitable solvents or amphiphiles (see pp. 25-26).

Accordingly, Applicants respectfully request that this indefiniteness rejection be reconsidered and withdrawn.

Claim 65 was rejected as being vague and indefinite because the phrase "pure or purified antigen" utilizes the relative terms "pure or purified." The Office Action alleges that one of skill in the art would not realize to what degree the antigens must be purified.

Applicants respectfully aver that the claim clearly indicates that all that is required is that the antigen is purified from the other molecules such as proteins, carbohydrates, and lipids in complex solution with the antigen. In its normal usage, the term "pure" means "unadulterated, free from admixture or contamination with extraneous matter" (Stedman's Medical Dictionary, 26th Ed., Williams and Wilkins, 1995). The term "purified" in normal usage means "to remove unwanted constituents from a substance" (McGraw-Hill Dictionary of Scientific and Technical Terms, 5th Ed., McGraw-Hill, New York, 1994). Therefore, the meaning of the phrase "pure or purified" would be readily understood to those of skill in the art.

The specification at Examples 11-13 provide methods by which an antigen can be partially purified, and indicates that pure antigen can be obtained from common commercial

sources, which provide the degree of antigen purity. Furthermore, Figure 4 shows the effects of antigen purity on antigen efficacy. Thus, one of skill in the art would readily understand from the teachings of the specification and common knowledge within the art what the term "pure or purified" means and to what degree of purity the claim is referring.

Accordingly, Applicants respectfully request that this indefiniteness rejection be reconsidered and withdrawn.

Claim 67 was rejected as being vague and indefinite due to the phrase "at least one injectable dose." The Office Action alleges that the term "injectable dose" is unclear because it does not clearly indicate what limits Applicants intend by the term. Applicants traverse this rejection.

The specification states that "the kit comprises at least *one injectable dose* of the antigen" (see Specification, pg. 27, first paragraph; pg. 28, first paragraph). According to the specification, an "injectable dose" refers to the amount of antigen that would be normally be injected into the subject. Thus, those of skill in the art would understand upon reading the specification that the term "injectable dose" refers to the dose of the particular antigen injected into a subject.

Accordingly, Applicants respectfully request that this indefiniteness rejection be reconsidered and withdrawn.

5. Claim Rejections Under 35 U.S.C. § 103

Claims 37, 39-45, 47-48, 50, 55, 58-60, and 62-67 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Glenn *et al.* (PCT Publ., WO 98/20734) ("Glenn") in view of Paul *et al.* (1995) *Vaccine Res.* 4: 145-164 ("Paul"). Applicants traverse this rejection.

For a claimed invention to be obvious under 35 U.S.C. § 103, the references forming the basis for an obviousness rejection must teach or suggest all of the claim limitations of the claimed invention. (*In re Royka*, 490 F.2d 981 (C.C.P.A. 1974)). Also, *it is improper for the purposes of an obviousness rejection to combine references where the references teach away from their combination* (MPEP § 2145 X.D.2). Moreover, there must be a motivation to combine, either explicitly or implicitly, the teachings of references (MPEP § 2143.01).

Applicants' invention, as recited in Claim 37, is directed to a transdermal vaccine comprising a transdermal carrier, the carrier comprising a penetrant including a minute fluid droplet surrounded by a coating of one or more layers of at least 2 substances. Applicants' claimed transdermal vaccine further comprises a compound that induces cytokine or anti-cytokine activity and an antigen or mixtures of different antigens and/or an allergen or mixtures of different allergens.

Paul teaches transferosome compositions that include bovine serum albumin as the substance that the transferosome is transporting across the barrier. Paul does not teach or suggest a vaccine composition comprising an antigen or allergen.

Glenn discloses transdermal vaccines of tetanus toxoid and IL-12. Glenn does not teach or suggest the combination of its transdermal vaccines with the compositions of the claimed invention. Moreover, Glenn explicitly distinguishes itself from Paul.

Applicants respectfully aver that there is no motivation to combine the references, either explicitly or implicitly. Paul concludes that the transferosomes taught in the reference were sufficient to cross epicutaneous barriers (pg.160, second paragraph). Likewise, Glenn teaches that bacterial ADP-ribosylating exotoxins are sufficient systems for crossing epicutaneous barriers (pg. 11, lines 9-16). Thus, one of skill in the art would not be motivated to combine the references because the references teach two systems that are independently and exclusively adequate for the introduction of proteins across barriers.

Furthermore, Applicants respectfully assert that the references teach away from the claimed application. Glenn and Paul both state that "[i]t is thus impossible to *immunize epicutaneously* with simple peptide or protein solutions" (see Glenn *et al.* pg. 2, lines 24-28, *quoting* Paul *et al.*, pg. 145). Both references also teach that dermally applied liposomal or mixed micellar immunogens are "biologically as inactive as simple protein solutions" (see Glenn *et al.* pg. 2, lines 24-28, *quoting* Paul *et al.*, pg. 145). Glenn further distinguishes itself from Paul by explicitly contrasting its invention from the cited art, of which Paul is one of the references cited by Glenn (pg. 3, line 29). Therefore, both references teach away from any combination that would yield the claimed invention.

Accordingly, as there is no motivation to combine the cited references, Applicants' claimed invention (Claim 37) is not obviated y the combination of these references. Thus, Applicants respectfully request that this 103 rejection be reconsidered and withdrawn.

Likewise, as dependent Claims 39-45, 47-48, 50, 55, 58-60, and 62-67 contain all of the limitations of independent Claim 37, Applicants respectfully request that their rejection should also be reconsidered and withdrawn.

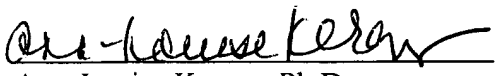
CONCLUSIONS

In view of the arguments set forth above, Applicants respectfully submit that the outstanding rejections contained in the Office Action mailed on May 25, 2006 should be reconsidered and withdrawn.

The time for responding to this action has been extended to October 25, 2006 by the accompanying Petition for a Two Month Extension of Time and payment of fee. No additional fees are believed to be due in connection with this response. However, please charge any underpayments or credit any overpayments to Deposit Account No. 08-0219.

If the Examiner believes that any further discussion of this communication would be helpful, please contact the undersigned at the telephone number provided below.

Respectfully submitted,



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